UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/801,648	03/17/2004	Hsiang-Fu Kung	V9661.0074	2232

32172 7590 09/20/2006

DICKSTEIN SHAPIRO MORIN & OSHINSKY LLP
1177 AVENUE OF THE AMERICAS (6TH AVENUE)
41 ST FL.
NEW YORK, NY 10036-2714

EXAMINER	
KELLY, ROBERT M	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 09/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/801,648	KUNG ET AL.	
	Examiner	Art Unit	
	Robert M. Kelly	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 June 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9 and 31-47* is/are pending in the application.

4a) Of the above claim(s) *1-9,17-22,27,28 and 34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-16,23-26,29-33 and 35-47* is/are rejected.

7)☒ Claim(s) *13-16 and 23-26* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 June 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/30/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment and argument of 6/30/06 is entered.

Claims 10-12 have been cancelled.

Claims 31-47 are newly added.

Claims 13, 15-16, 23, 25-26, and 29-30 are amended.

Claims 1-9 and 31-47 are presently pending.

Election/Restrictions

Claims 1-9, 17-22, and 27-28 remain withdrawn from prosecution as being drawn to non-elected inventions, as per the election of 12/21/05 and Official Action of 3/1/06.

New Claims 31-47 are within the scope of the elected invention.

This application contains claims 1-9, 17-22 and 27-28, drawn to an invention nonelected with traverse in the response of 12/21/05. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Due to the amendments, specifically claiming non-bone disorders, the following further restriction requirement is made, over and above the previously elected invention:

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 13-16, 23-26, 30-33, and 34-47, drawn to methods of treating disease/disorders of the bone and expressing BMP, classified in class 514, subclass 44.

II. Claims 30, 31, 32, and 34, drawn to methods of treating cancer, classified in class 424, subclass 93.1.

The inventions are distinct, each from the other because of the following reasons:

Inventions I and II are patentably distinct. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different designs, modes of operation, and effects (MPEP § 802.01 and § 806.06). In the instant case, the different inventions are not disclosed as capable of use together, and further require distinct structural requirements to effect distinct therapies. To wit, the specification discusses BMP and treatment of bone disorders in general, by growing new bone, while it provides some discussion of other factors for treating cancer, e.g., p53. Moreover, the physiology of bone disorders is distinct from that of cancer, and therefore, the functions of bone morphogenetic protein would not provide the functions required for treating cancer. Moreover, because of the distinct structures required in bone disorders and that of cancers, it would pose a serious burden on the examiner to search and examine any two inventions together.

Claim 29 link(s) inventions I and II. The restriction requirement of the linked inventions is subject to the nonallowance of the linking claim(s), claim 29. Upon the indication of allowability of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise requiring all the limitations of the allowable linking claim(s) will be rejoined and fully examined for patentability in accordance with 37 CFR 1.104 Claims that require all the limitations of an allowable linking claim will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier.

Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

Applicant(s) are advised that if any claim(s) including all the limitations of the allowable linking claim(s) is/are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. In re Ziegler, 443 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

Newly submitted claim 34 is directed to an invention that is independent or distinct from the invention originally claimed for the reasons provided above.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 34 withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 13-16, 23-26, 29-33, and 35-47 are presently considered.

Specification

The disclosure remains objected to because of the following informalities: Applicant's specification contains a table of contents, listing the pages of the specification as filed, however, such specification, if it is issued as a publication or patent, will not translate those pages into proper reference to columns and paragraphs, for

reasons of record. Hence, Applicant is requested to remove such table of contents, however, the Examiner thanks Applicant for the easy accessibility to the subject matter provided by such table of contents.

Appropriate correction is required.

In light of the amendment to the brief description of the drawings, the objections for the following informalities: In the brief description of the drawings, there is no description for drawing 8F, and the reference to the drawings of figure 7 is written as a description of only figures 7A and 7F, not 7A through 7F, are withdrawn.

The amendment filed 6/30/06 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: Applicant's amendment to the specification limits SEQ ID NO: 1, which is taught to be a specific sequence encoding a BMP (specification, p. 6). However, no support for the truncated sequence is provided by the specification and/or claims as filed.

Applicant is required to cancel the new matter in the reply to this Office Action.

Response to Argument – Objections to specification

Applicant's argument of 6/30/06 has been fully considered but is not found persuasive.

Applicant argues that SEQ ID NO: 1 is taught to encode SEQ ID NO: 2, and hence the truncation of such sequence is possessed (p. 7).

Such is not persuasive. What applicant has shown is that it would be obvious to use the portion of the sequence encoding SEQ ID NO: 2. However, obviousness does not suffice for possession. Moreover, Applicant is reminded that it is Applicant's duty to demonstrate such possession.

Drawings

In light of Applicant's submission of new drawings and petition, meeting the proper requirements for the presence of color photographs, the objections to the drawings are withdrawn.

DAVE TRONG NGUYEN
SUPERVISORY PATENT EXAMINER

Applicant's petition for color photographs is accepted.

Claim Objections

Claims 13-16, and 23-26 are objected to because of the following informalities:

Claims 13 and 23 each recite "in a body area of an immunocompetent subject where bone regeneration is required". The way limitation is written, it is not clear if the body area requires bone regeneration; however, given that the Artisan would understand what is being claimed, the claim is not rejected. It would be remedial to amend the limitation to recite "in a body area where bone regeneration is required, in an immunocompetent subject".

Claims 14-16 and 24-26 are objected to for depending from an objected to base claim and not overcoming the basis of rejection.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 13-16, 23-26, and 29-33, and 35-47 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for reasons necessitated by the amendments.

Claims 13, 23, 29, 35, and 41 each recite local administration. The metes and bounds of such local administration are unclear. Applicant's only supplied statement is that it includes administrations to any blood vessel that feeds the target tissue, spraying or applying a suppository to the afflicted tissues (SPECIFICATION, p. 7), but such is written in comprising language and therefore, it is unclear how close an administration must be to be considered local.

Claims 14-16, 24-26, 30-33, 36-40, and 42-47 are rejected for depending from a base claim and not overcoming the lack of clarity in such base claim.

Claims 13, 23, 29, 35, and 41 each recite "where bone regeneration is required". The metes and bounds of the term "required" are unclear. Without a reason for a requirement, e.g., to cure a disorder, it is unclear what situations require bone regeneration.

Claims 14-16, 24-26, 30-33, 36-40, and 42-47 are rejected for depending from a base claim and not overcoming the lack of clarity in such base claim.

Claim Rejections - 35 USC § 112 – new matter

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13-16, 23-26, 29-33, and 35-40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 13-16, 23-26, and 35-40 specifically encompass SEQ ID NO: 1. Moreover, Claims 29-34 encompass SEQ ID NO: 1 within their scope, as SEQ ID NO: 1 is the single specifically discussed nucleotide sequence encoding a therapeutic gene product.

Applicant's amendments of 6/30/06 amend SEQ ID NO: 1 to truncate the non-coding sequences in the sequence. However, Applicant has provided no support for possession of such, and any arguments are directed to obviousness (See Objection to Specification, ABOVE).

Hence, these Claims are rejected for comprising new matter.

Claim Rejections - 35 USC § 112 – written description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13-16, 23, 25-26, and 29-47 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant's claims now encompass administration of the vector(s) locally to a body area. However, no explicit or support for such limitation is provided by Applicant. Moreover, the scope of administration is very broad (see rejection under 35 USC 112, second paragraph), encompassing any administration which leads to the transformation of the cells.

Moreover, while providing broad statements that are so broad as to be indefinite (SPECIFICATION, p. 7), the only specific discussion is that of direct administration to muscle (EXAMPLES).

Hence, given the broad scope encompassed by the claims, being so broad as to be indefinite, and given that Applicant has only demonstrated support for direct administration, the Artisan would not understand Applicant to have possessed the invention as claimed, but only direct administration.

Claim Rejections - 35 USC § 112 – enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13-16, 23-26, and 29-47 remain rejected and/or are newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, for reasons of record, and the restatement below. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The analysis is again repeated below, further addressing the newly claimed subject matter.

The Law

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by Applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ.2d at 1404. Such factors are:

(1) The breadth of the claims;

(2) The nature of the invention;

(3) The state of the art;

(4) The level of one of ordinary skill in the art;

(5) The level of predictability in the art;

(6) The amount of direction and guidance provided by Applicant;

(7) The existence of working examples; and

(8) The quantity of experimentation needed to make and/or use the invention.

These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention, such experimentation being found undue as it would essentially constitute inventing Applicant's claimed invention for Applicant, and that, therefore, Applicant's claims are not enabled for their fully claimed scope.

The Breadth of the Claims

Claims 13-16 and 30 encompass a method of treating any disease or disorder in any subject with any bone regeneration requirement, comprising administering locally, by any route, an AAV vector comprising a transgene comprising a promoter operably linked to SEQ ID NO: 1 (the human nucleic acid sequence encoding BMP-2) or a sequence encoding SEQ ID NO: 2(the human protein sequence of BMP-2). Claims 14-15 limit the promoter to a BMP promoter or the CAG promoter, respectively. Claim 16 limits the administration to direct administration to skeletal muscle. Claim 32 limits the subject to human. Claim 33 limits the disorder to one of six.

Claims 23-26 parallel claims 13-16, but also require similar administration of an Adenoviral vector comprising the same transgenes. (It is noted that the presently examined invention is limited to this more complicated embodiment at present, See Restriction requirement of 11/15/05 and response of 12/21/05.) Claim 33 limits the disorder to one of six. Claim 30 requires the amount of AAV vector administered to be higher than the amount of Adenoviral vector.

Claims 29-32 and 34 encompass a method of treating any disease or disorder in any subject comprising administering locally, by any route, two vectors: an AAV vector comprising a promoter operably linked to any therapeutic gene product encoding

sequence, and an adenoviral vector comprising a promoter operably linked to a second therapeutic gene product encoding sequence. Claim 30 requires the amount of AAV vector administered to be higher than the amount of Adenoviral vector. Claim 31 requires the promoter to be the CAG promoter. Claim 32 requires the subject to be human.

Claims 35-39 encompass a method for expressing BMP for new bone formation in any body area of a subject, comprising administering locally, by any method, to the body area an effective amount of a nucleic acid encoding AAV and a promoter operably linked to a sequence encoding BMP. Claim 36 limits the BMP to BMP-2. Claim 37 limits the coding sequence of BMP to SEQ ID NO: 1 or encoding SEQ ID NO: 2. Claim 38 limits the promoter to the BMP promoter of the protein encoded. Claim 29 requires the CAG promoter. Claim 40 requires the administration to a skeletal muscle.

Claims 41-47 encompas a method of expressing BMP for new bone formation in any body area of a subject, comprising administering locally, by any method, to the body area, a nucleotide encoding an AAV viral vector and a promoter linked to a sequence encoding BMP and an adenoviral vector and a promoter linked to a sequence encoding BMP. Claim 42 limits the encoding sequence of the BMP to SEQ ID NO: 1 or encoding SEQ ID NO: 2. Claim 44 limits the amount to a non-toxic and non-immunogenic amount. Claim 45 limits at least one promoter to a BMP promoter. Claim 46 limits at least one promoter to CAG. Claim 47 limits administration to skeletal muscle administration.

These claims are broad because of the range of diseases and disorders encompassed, the levels of therapy, the variety of subjects, and the range of administration routes. Such breadth must necessarily require a large amount of

information to be disclosed by the specification, in view of the art, such that the Artisan would be able to reasonably predict the embodiments encompassed by the claimed invention that would effect therapy, without having to perform such experimentation to confirm whether or not any specific embodiment would be effective for such treatment.

Furthermore, these claims are broad for encompassing administration of nucleic acids comprising a viral vector, along with separate administration of a promoter operably linked to a coding sequence. Such administrations are doubled, due to the presence of a second viral vector in claims 23-26 and 29-30.

Furthermore, the new claims are broad for the tissues which are transformed by the range of administration routes.

Lastly, the claims to new bone formation, given the teachings throughout the specification, are necessarily required to be enabled for therapy. Such is because the specification only discusses that the reasons for performing such methods are to perform therapy, and the Artisan would therefore understand these claims to be drawn to therapy even though not specifically requiring therapy.

The Amount of Direction and Guidance Provided by the Specification

The specification discusses broadly that the invention is in the field of treating preventing, treating, managing, or ameliorating diseases or disorders of all types (pp. 1-2), a broad discussion of the advantages and disadvantages of AAV vectors (pp. 2-3), a discussion of studies of the use of BMPs to effect bone repair and healing (pp. 3-4), a summary of the claimed invention and methods provided in the experimental section (pp. 4-7), definitions (pp. 7-11), a brief description of the figures (pp. 11-13), a discussion of orthotopic bone formation via Applicant's methods and cocktails of mixtures of viral

vectors to effect therapy (pp. 14-15), methods of constructing the vectors (pp. 15-19), pharmaceutical compositions, which may be formulated for any route of formulation (pp. 19-23), methods for performing many envisioned treatments, ranging from brain, lung, kidney, and hematopoeitic injury to treating bone disorders, which may require other transgenes than BMP transgenes (pp. 24-25), methods of administration to any animal (pp. 25-28), a broad review of gene therapy, which Applicant envisions as being applicable to the invention (pp. 28-33), a demonstration argued to prove therapeutic or prophylactic utility, wherein C2C12 cells are tested for proliferation, and expression of transgenes by antibody analysis, and proposed testing of the agents in suitable animal models (pp. 33-34), and a discussion of the LD50 determinations for any particular protein (pp. 34-35).

Further, it is apparent that Applicant's local administration is not direct administration, as it may include, for example, administration to a vein leading to the site (p. 7, paragraph 2), or, by extrapolation, by any method which leads to the required transformation.

However, such broad description does not provide the specific direction and guidance the Artisan would require to reasonably predict the working embodiments, because the Artisan would not be able to reasonably predict that for any particular disorder or disease, in any particular animal type, whether administration of any particular AAV vector, encoding any particular BMP would effect any particular type therapy, through any route of administration. Such is because the transgene is not reasonably predicted to be therapeutic in any particular disorder, and for those it is applicable to, it is not reasonably predicted that enough of the target cells will be

transformed and express enough stable and functional mRNA and protein therefrom, for a long enough period of time to effect treatment. Such will be shown below.

Moreover, no direction or guidance is given for the administration of a viral vector and a promoter operably linked to a coding sequence, except in the context of a viral vector comprising a nucleic acid comprising a promoter operably linked to a coding sequence.

The Existence of Working Examples

Example 6.1 demonstrates the making of AAV2 vectors comprising the human BMP-2 transgene operably linked to the CAG promoter. Example 6.2 demonstrates the expression of BMP-2 in C2C12 cells via transfected vectors of Example 6.1. Example 6.3 demonstrates in vitro transduction of C2C12 cells with consequent alkaline phosphatase activity increases in the cells. Example 6.4 demonstrates transsfection of hind limb muscle of rats with the vectors of the invention, and subsequent harvest of the muscle tissue after 1-8 weeks. Example 7.1 demonstrates increased BMP-2 expression in C2C12 cells, post transfection with the vector. Example 7.2 demonstrates that the C2C12 cells show an osteoblast shape phenotype after transfection. Example 7.3 demonstrates that the same cells show increased alkaline phosphatase activity, which Applicant argues demonstrates obvious differentiation of myoblasts into osteoblasts. Examples 7.4 and 7.5 demonstrate the formation of bone-like structure in the muscle tissue of rats after injection, intramuscularly, of AAV vectors alone, or with Adenoviral vectors, each vector comprising the transgene for BMP-2.

However, given Applicant's demonstration of inappropriate bone-like structure formation, the Artisan would not reasonably predict treatment of anything. Such

inappropriate bone formation is not only unrelated to treating any disorder or disease, but appears to only have use in the study of the molecular mechanisms of bone formation, with the future goal of effecting treatment of bone disorders.

The Nature of the Invention

Applicant's invention is in the nature of gene therapy. Gene therapy is generally not enabling of new inventions in the field.

With regard to gene therapy, while progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be a difficulty as supported by numerous teachings available in the art. For example, Deonarain (1998) Expert Opin. Ther. Pat., 8: 53-69, indicates that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequeate levels for a long enough period of time" (p. 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (p. 65, CONCLUSION). Verma (1997) Nature, 389: 239-242, reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (p. 240, sentence bridging columns 2 and 3). Verma states that "The Achilles heel of gene therapy is gene delivery and this is the aspect we will concentrate on here. Thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression ... The use of viruses (viral vectors) is a powerful technique,

because many of them have evolved a specific machinery to deliver DNA to cells. However, humans have an immune system to fight off the virus, and our attempts to deliver genes in viral vectors have been confronted by these host responses (e.g., p. 239, col. 3).

Further, Eck et al. (1996) Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, NY., pp. 77-101, states that the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced, are all important factors for a successful gene therapy (e.g., bridging pp. 81-82). In addition, Gorecki (2001) Expert Opin. Emerging Drugs 6(2): 187-98) reports that "the choice of vectors and delivery routes depends on the nature of the target cells and the required levels and stability of expression" for gene therapy, and obstacles to gene therapy *in vivo* include "the development of effective clinical products" and "the low levels and stability of expression and immune responses to vectors and/or gene products" (e.g., ABSTRACT).

Further, these conclusions continue to exist, even in the Art examining the nature of the invention after the date of Applicant's filing. To wit, for example, Worgall (2005) Pediatr. Nephrol., 20: 118-24 recognizes that a number of hurdles must still be overcome to make gene therapy applicable for human diseases (ABSTRACT). Some of these

problems include lack of persistent expression (ABSTRACT), targeting of any specific tissue (p. 118, col. 2), the fact that any specific serotype of AAV may not even infect the target tissue of interest, although AAV type 1 is known to infect muscle well (p. 120, col. 2, paragraph 2), problems with immune responses, not only to the vector, but to the expressed transgene (p. 121, paragraph bridging columns). Moreover, even if particular vector can transform the specific organ, any specific cell type within that organ may prove problematic (pp. 121-22, paragraph bridging). In concluding, Worgall notes that gene therapy has in general come a long way since its inception, but still faces significant challenges before it can become reasonably predictable for human gene therapy, and, by analogy, to any animal gene therapy (CONCLUSION). What Worgall believes will be required for such is the development of new vector systems, and therapy strategies for a variety of acquired and inherited diseases, the efficacy of such systems needs to be vigorously studied before such can be reasonably predictable (Id.).

Another, exacerbated by the fact that the fact, as shown in Worgall that specific serotypes of AAV may not transfect the tissue of interest is that any particular patient may already be immune to the specific vector type used in performing gene therapy, requiring use of another serotype which may not tranfect the target cells of interest, thereby negating therapy (Nathwani, et al. (2004) Vox Sang., 87: 73-81, p. 75, paragraph bridging columns). Moreover, various forms of administration may lead to wide dissemination and transduction of non-target tissues, leading to side effects, such as development of neutralizing antibodies to the transgene product, or severe inflammatory responses, which may negate any therapeutic effect (p. 78, last paragraph). In conclusion, Dr. Nathwani concludes, gene therapy is relatively new, and requires the

researcher to take stock of the current problems and invest time into unraveling the biological mechanisms that underlie viral entry into a cell, transport to the cell nucleus, and persistent of genome, as well as long term expression of the proteins encoded (p. 79, paragraph bridging columns). Again, this is echoing the nature of the invention shown by the earlier art of record, that it is not reasonably predictable that any particular vector, administered by any particular route, will transform enough of the target tissue, and do so for a long enough period of time, to express the transgene for a long enough period of time to effect any particular treatment.

The State of the Prior Art

The majority of the prior art for gene therapy involving BMPs involves the regeneration of bone, and there exists no art of record that such BMPs can be used to treat any disorder or disease. To wit, for example, the Art of record does not demonstrate that BMPs expression in any particular tissue would effect treatment for Parkinson's disease or muscular dystrophy, osteopetrosis, or even cancer treatment. At best, Applicant appears to rely on the fact that BMPs are members of the super-family of TGF cytokines, and as such, argues that BMPs are therefore TGF cytokines. However, being a member of the super-family does not mean that BMPs are cytokines for treatment of any particular disorder. For example, it has long been known that the BMP's are classified in smaller subgroups of BMP, based on structure (Leong, et al. (1996) Int. J. Biochem. Cell. Biol., 28(12): 1293-96, p. 1293, paragraph bridging columns), which appear to have distinct effects, and which effects differ depending on the animal they are acting within (Id.). Hence, by such argument, these proteins also being members of receptor-binding proteins, should effect all signaling pathways in the cell. In essence, simple classification

does not mean that these proteins would have any other effect, except those known effects. To wit, even within the small group of BMPs, it is clear that particular members of the genera of BMPs are not reasonably predicted to encourage, but actually block, bone formation (Derner, et al. (2005) Clin. Podiatr. Med. Surg., 22: 607-18, p. 611, first paragraph). Hence, within this closer related group of BMPs, even bone formation function is not common to each of the proteins of the genera. Further, in many cases, when treated by known-effective protein BMP therapy, many patients do not fuse the newly-rendered bone to the present bone (p. 612), and lastly, Derner recognizes that gene therapy methods hold promise, but similarly recognizes that it is not yet reasonably predictable with regard to efficacious treatments (pp. 615-16, paragraph bridging).

The specific field of gene therapy to effect bone repair is essentially synthesized by one of the early success stories in the field, disclosed by Alden, et al. (1999) J. Neurosurg., Spine 1, 90 : 109-14. One of the most important aspects of this is that when the vectors are injected into the musculature, bone formation is not the normal bone, but is limited to the site of injection, not within the bone (p. 110, paragraph bridging columns). Moreover, it is apparent that the concentration of the BMP is paramount to the effects it will stimulate, requiring the range of micromolar concentrations to promote bone differentiation (pp. 112-133, paragraph bridging columns), and hence, it is not reasonably predictable that the concentrations made in muscle would induce bone formation distant to the site of injection. Moreover, the new bone formed does not fuse with the bone already present, being separated by a cartelagenous tissue, which may be due to expression in the periosteum of other factors that prevent such fusion (p. 113, paragraph 1). Hence, if these bones do not fuse, it is not reasonably predictable that the

newly formed bone would become part of the skeletal structure to help with any particular disorder. It is further noted that such lack of fusion is completely distinct from that seen in protein therapy, demonstrating that protein therapy is not reasonably predictive of therapy by gene therapy (Id.). In fact, Alden recognizes that many issues still need to be addressed to make such therapy reasonably predictable, including inter-species differences, the fact that may distinct BMPs may be required to be expressed, along with possible other factors, and lastly, it is clear that attenuation of expression remained a problem (p. 113 in general). Therefore, from Alden, the Artisan would not reasonably predict treatment across species, or with any particular vector, to treat any particular condition, as even within the BMPs, the concentrations required for any particular effect need to be carefully maintained, and even then, contrary to protein therapy results, the bone formed does not appear to fuse with endogenous bone.

Further, with regard to the various tissues, it is not reasonably predictable in the art that administration to any tissue will produce bone formation. To wit, Riley, et al. (1996) Clin. Orthopaed. Relat. Res., 324: 39-46, demonstrates that any particular BMP may cause other effects than bone formation in any specific tissue (e.g., p. 41, column 2). Hence, if the administration was to another tissue, e.g., neural tissue, bone formation would not be reasonably predicted, but instead, neural embryogenesis. This is further exacerbated for the scope of BMPs claimed, which are acknowledged by Alden (ABOVE) to have many varied functions.

Lastly, with regard to immunogeneicity and toxicity, by encompassing toxic and immunogenic amounts, the Artisan would reasonably predict that those embodiments

would negate any therapeutic effect/bone formation due to immune responses and/or killing of the cells.

The Level of Skill in the Art

The level of skill in the art is high, being that of a Ph.D. or M.D., however, given that the field is still generally not found reasonably predictable, as evidenced by the other sections, the Artisan would still not reasonably predict any therapy for any particular disorder or disease in any particular animal.

The Level of Predictability in the Art

The level of predictability in the art is such the Artisan would not reasonably predict that any disorder or disease could be treated, ameliorated, or prophylactically treated by the claimed methods. Such is because the diseases are not fully understood, and often do not even appear to involve BMP, and further because any particular BMP, delivered by AAV vector, by any particular route, is not reasonably predicted to transfect enough of the target tissues, in large enough amounts, and express enough stable and functional mRNA and protein therefrom, for a long enough period of time to effect treatment. Moreover, even for bone treatments, some disorders, like osteopetrosis, would be exacerbated by the methods, and due to the localized nature of the effected bone formation, and its apparent inability to fuse with normal bone, when performed by gene therapy methods, the Artisan could not reasonably predict any particular working embodiment. Further, this is exacerbated by the fact that the Artisan would not reasonably predict treatment of any other animal, from the treatment of any particular species. The Art, and Applicant's specification appear to be limited to demonstrations of gene therapy in mice and rats, however, such is not even therapy, much less predictive of

treating any other animal. Ectopic bone formation simply not known to be wanted in any therapy of record, and appears not to be related to any treatment.

The Amount of Experimentation Required to Practice the Invention

The Artisan would have to perform experimentation to determine the disorders, routes of treatment, types of BMP, and whether cocktails of differing AAVs are required to effect any particular treatment, in any particular animal. Moreover, this is exacerbated by the fact that treatment of one particular species is not predictive of treatment in another, and the fact that those gene therapy experiments of record demonstrate a lack of fusion of the newly-made bone with that of the endogenous bone. Lastly, experimentation would be required for determining the scope of treatments that could be effected via the various routes, wherein a viral vector and a separate promoter operably linked to a coding sequence, which is doubled by the second viral vector and promoter operably linked to a coding sequence in some claims. Hence, more experimentation would be required. Next, for the scope of administrations encompassed, and the scope of tissues in which bone formation may be induced, the various administrations and tissues would have to be tested to determine the efficacy of the method, due to the lack of predictability in the art. Lastly, for the scope of toxic and immunogenic administrations, the artisan would have to experiment to determine which of those embodiments would achieve the purpose of the methods prior to negation of those cells expressing the protein due to toxicity or immunogenic response.

Such experimentation is considered undue, essentially because it amounts to inventing Applicant's claimed subject matter for Applicant.

Conclusion

Because of the amount of experimentation, Applicant's claimed subject matter is not enabled for its fully claimed scope.

Response to Argument – enablement

Applicant's response of 6/30/06 has been fully considered but is not found persuasive.

Applicant's response appears to be their own analysis, rather any showing of how the amended the claims actually overcome the Examiner's previous rejection, and therefore, the Examiner will do his best to determine what Applicant is saying in each portion of the response, in order an answer any implied argument.

Applicant implies that they are enabled, because the combined use of the two vectors appears to provide higher levels of expression and lower levels of immune response than the use of a single vector (pp. 16-17).

Such is not persuasive. Simply being better than a failed method does not demonstrate that the method will work in a reasonably predictable fashion for the breadth claimed. Moreover, if the invention is enabled due to the use of the combined vectors, Applicant appears to be implying that those claims encompassing a single vector administration are not enabled.

Applicant argues that their demonstration of ectopic bone formation is enabling for the claimed invention (pp. 17-18).

Such is not persuasive. Simply providing does not overcome the basis of rejection for therapy, and such has been addressed in the official action of 3/1/06 and readdressed above.

Applicant argues that AAV vectors have been approved in China for gene therapy of head and neck cancer, and further their method is more efficient, requiring less vector and less immunogeneicity, and hence, the claims are enabled (pp. 19-20).

Such is not persuasive. China is not the United States, and medical testing is not what the United States Patent Office bases its decisions on. The Examiner has given reasons why in the Official Action of 3/1/06 and readdressed above. Whether or not a single vector is allowed for some form of gene therapy in some country is not a concern of the Examiner. Applicant must demonstrate such to be reasonably predictable for the invention elected.

Applicant argues that direct administration is enabled, for local development of new bone, and hence, the rejections for forms of administration are overcome (pp. 20-21).

Such is not persuasive. As demonstrated above, and in the rejection for lack of clarity, it appears that local administration may still be distal from the site. The Examiner has limited any enabled scope to direct administration, and to muscle tissue, due to the new claims presented, and for reasons given above. Local administration to an artery, or for that matter skin or other places, which leads to such transformation is simply not reasonably predictable.

Applicant argues that from their results, it would be routine experimentation to treat the various diseases (pp. 21-22).

Such is not persuasive. Applicant has failed to demonstrate that it is reasonably predictable for any species to have therapy, that the bone fuses with endogenous bone,

that the administration will be effective, etc., as is again demonstrated above. As such, it is still not reasonably predictive of any disease/disorder.

Applicant argues they provide information for the scope of treatment (10 fold enhancement over AAV vector alone); route of administration (local) and compositions (AAV and AdV vectors), and any further experimentation is routine (p. 22).

Such is not persuasive. Applicant has not provided the information required for the scope of treatment (which also includes the disorders, the tissues, the levels of expression required for any particular BMP/disorder, etc., as shown above and in the previous official action), the route of administration (such also encompasses any route which transforms the tissue, and requires the tissues which can be so-treated) and the compositions (which requires the relative amounts required to obtain the various toxicity and immunogenicity requirements). Such would require undue experimentation of the Artisan, because he/she would have to experiment to reasonably predict the working embodiments.

Claims Free of the Prior Art

The claims examined are free of the Art for the elected invention.

While the Art generally recognized that Adenoviral vectors could be used to produce ectopic bone in muscle (e.g., Alden, et al. (1999) Human Gene Therapy, 10: 2245-53, ABSTRACT), the Art also recognized that these vectors produced immune responses which could preclude production of such bone (e.g., Id.). Moreover, while the Art already recognized the ability of Adenoviral vectors to provide for increased AAV transfection efficiency of muscle (Malik, et al. (2000) J. Virol., 74(8): 3555-65, ABSTRACT), and the Art also recognized the ability of AAV to transform, *inter alia,*

muscle tissue (e.g., Abadie, et al. (2002) Gene Therapy, 9: 1037-43, ABSTRACT), The Art does not teach or fairly suggest the cotransformation of cells to product bone, via the claimed dual-vector system. Such is because the Art general recognizes that the immune responses to the Adenoviral vectors would be likely to preclude bone formation, as taught in the Art. Hence, there would be no motivation to combine the Art.

Further, to support such analysis, the first art to demonstrate this ability to work in immunocompetent animals is the inventor's art: Chen, et al. (2004) Biochem. Biophys. Res. Commun., 317(3): 675-81.

Conclusion

No Claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert M. Kelly, Art Unit 1633, whose telephone number is (571) 272-0729. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Robert M. Kelly, Ph.D.
Examiner, USPTO, AU 1633
Patents Hoteling Program
2C55 Remsen Building
(571) 272-0729